for this amendment can be found on page 14, lines 18-27. Claim 12 has been amended to correct an improper dependency by incorporating the language of claim 1 into the body of claim 12; this claim has been further amended to recite that all peptides and polypeptides are biologically active. Claim 14 has been amended to delete duplicative peptides and polypeptides. No new matter is added by these amendments.

Restriction Requirement

Applicants hereby confirm their election of Group II (claims 10-14 and 17-20) in response to the restriction requirement previously imposed by the Examiner.

Claim Objections

Claims 10 and 12 have been amended herein to correct the dependency to a non-elected group. Claim 14 has been amended to delete duplicative peptides and polypeptides.

Rejection Under 35 USC, Section 112

Claim 11 has been rejected under 35 USC, Section 112 as allegedly not enabled by the specification. According to the Examiner, claim 11 is directed to novel vectors that are essential to the claimed invention and thus the vectors must be obtainable by a repeatable method set forth in the specification. The Examiner further states that the specification does not disclose a repeatable process for obtaining the vectors.

In response, Applicants submit that the claimed vectors can readily be prepared by following the detailed teachings set forth in Applicants' specification as, for example, on pages 25-35 of the specification. A description of vector components and methods for preparing suitable vectors is provided therein, and a skilled artisan could prepare any of the claimed vectors by simply following these teachings. However, solely in the interest of advancing prosecution herein, Applicants enclose herewith a statement signed by their attorney of record indicating that exemplary vectors of the present invention have been deposited under the Budapest Treaty.

Claim 11 has been rejected as allegedly not supported by the specification for the embodiment directed to splice variants. According to the Examiner, the specification does not provide the genomic DNA sequence of beta secretase, the identification of introns and exons, a rational and predictable scheme for isolation and characterization with the desired biological function, examples and sequence information of at least one splice variant, and sufficient guidance as to which of the "infinite possible choices" is likely to be successful.

In response, Applicants submit that the specification fully supports the claimed splice variants. As the skilled artisan would readily acknowledge, once the full length beta-secretase cDNA has been obtained, the genomic sequence can readily be obtained either by using the cDNA as a probe in a genomic library, or by conducting a sequence search on the Celera or other such human genomic sequence database using full-length cDNA as a "virtual probe". Upon obtaining the genomic sequence, introns can readily be identified, as those sequences will be present in the genomic clone but not in the cDNA clone. Once introns have been identified, exons will be immediately apparent. As is well known in the art, a splice variant is typically generated by alternate processing of intron sequences in an RNA transcript (see page 10, lines 33-36 of Applicants' specification), resulting in a protein that is missing one or more exons. Thus, there is no experimentation necessary to obtain a splice variant; only routine sequencing procedures are required. Once the splice variant(s) have been identified, they can easily be assayed for beta-secretase activity by following the detailed assays described by Applicants (see Applicants' specification, page 82, line 18 *et seq.*). Accordingly, the claimed biologically active splice variants are fully enabled by Applicants given the detailed teachings provided in the specification.

Claim 17 has been rejected as allegedly not enabled by the specification for "pharmaceutical compositions". According to the Examiner, the specification does not provide:

(1) the effective amount of beta secretase needed for use in the pharmaceutical composition;
(2) the disease(s) against which the composition is effective; and
(3) a demonstration of the desired effect of use in an art recognized animal model experiment.

In response to item (1) above, Applicants submit that claim 17 is fully enabled by the specification. As the skilled artisan will appreciate, the effective amount of beta secretase for use in a pharmaceutical composition will vary depending on therapeutic objectives such as the indication being treated, the route of

administration, and the condition of the patient. In addition, factors such as the weight of the patient must be considered. These factors and others are set forth in the specification for example on page 59, lines 8-26. As is stated on page 59, lines 27 *et seq.*, "As further studies are conducted, information will emerge regarding appropriate dosage levels for treatment of various conditions...and the ordinary skilled artisan...will be able to ascertain proper dosing."

In response to item (2) above, diseases in which beta secretase may be implicated and thus administration of a beta secretase molecule may be appropriate are set forth in the specification on page 76, lines 24-25, and on page 77, lines 5-6.

In response to item (3) above, Applicants respectfully remind the Examiner that there is no legal requirement for Applicants to provide any examples in the specification. Applicants have set forth several credible uses of the claimed compounds in the specification (as described in the paragraph above) and have provided suitable data to support such uses (see Example VI on pages 93 *et seq.*). Thus, there is no need (and no legal requirement) for Applicants to provide data using an art recognized animal model.

Claims 11 and 18 have been rejected as allegedly not enabled by the specification. According to the Examiner, no description has been provided of the modified polypeptide sequences, allelic variants and the splice variants, and the specification does not contain a description of the function of all of the polypeptide sequences derived from SEQ ID NOs: 4-6. The Examiner further alleges that the genus of claimed polypeptides is large and variable and thus many functionally unrelated polypeptides are encompassed by the scope of the claims. Finally, the Examiner asserts that the specification discloses only a single species of the claimed genus and this is insufficient to put the skilled artisan in possession of the attributes and features of all species within the claimed genus.

In response, Applicants first respectfully direct the Examiner to sections b and c of claim 11 wherein it is stated that the fragment/modified polypeptide be "biologically active". "Biologically active" is defined in Applicants' specification at page 14, lines 18-27 as having "the ability to cleave the APP Swedish mutation peptide EVKMDAEF". A description of the assay which measures such cleavage is set forth on pages 82 *et . seq.* of Applicants' specification. Given these teachings, the skilled artisan can readily identify those molecules that fall within the scope of Applicants' claims. Therefore, contrary to the Examiner's statement, the claimed molecules are not "functionally unrelated". The fact that the claimed

genus may encompass many molecules is irrelevant provided that Applicants have enabled the molecules, and, for the reasons set forth above, Applicants have indeed provided sufficient support for the molecules included in claims 11 and 18.

In view of the foregoing, Applicants respectfully request reconsideration and removal of the rejection under 35 USC, Section 112.

Rejection Under 25 USC, Section 102

Claims 11 and 18 have been rejected under 35 USC, Section 102 as allegedly anticipated by Chrysler *et al.* or Chapman *et al.* According to the Examiner, these references:

"disclose an enzyme with an identical activity of cleaving APP. From the functional and structural aspects disclosed in the reference it is highly likely that the enzyme, polypeptide sequence is identical to that of the instant application (99.9% identical to the amino acid disclosed by Chapman *et al.*...). Since there is no limitation placed on the number of changes that can be present in the polypeptide sequence, SEQ ID NO:4, for a [sic] allelic/splice variant or a derivative and since the applicant has not disclosed such amino acid sequences, Examiner [sic] believes that the enzyme and polypeptide disclosed in the reference is the same as that of the instant application." (page 12 of Official Action mailed 14 August 2000).

In response, Applicants respectfully assert that the rejection under Section 102 is improper. As the Examiner is aware, a reference cited as a 102 reference must teach every element of Applicants' claimed invention within the four corners of that reference. Such is not the case for the Chrysler *et al.* or the Chapman *et al.* references. While Chrysler *et al.* refers to a beta secretase enzyme, in fact no beta-secretase polypeptide sequence is provided in this reference; only the sequence of a beta-secretase substrate, APP, is set forth (Figure 6 and SEQ ID NO:17). Chrysler *et al.* do provide the sequence of a variety of peptides in their disclosure, however, none of these peptides are encompassed in the scope of Applicants' claims. In Chrysler *et al.*, SEQ IDs 2-4 are 13-19mers of a protein eluted from a gel and subjected to sequence analysis; SEQ IDs 5-7 are synthetic peptides corresponding to part or all of SEQ IDs 2-4; SEQ ID 8 is a synthetic consensus sequence of other peptides; SEQ IDs 9-10 are APP fragments; SEQ IDs 11-15 are synthetic peptide substrates; and SEQ ID 16 is also a synthetic peptide. No activity of any of the Chrysler *et al.* peptides is provided, and thus they do not fall within the scope of Applicants'

claim 11 as they are not shown to be "biologically active" as required by Applicants' claim 11. Thus, there is no way that this reference can be considered to be anticipatory to Applicants' claimed beta-secretase polypeptides, as its "four corners" do not contain the invention as claimed by Applicants.

Chapman *et al.* teach an aspartic proteinase-2 that differs from Applicants' SEQ ID NO:4 by an amino acid at Applicants' beta-secretase amino acid position 130. Applicants' beta secretase has a valine at this position, while Chapman *et al.* have a glutamic acid at this position. In addition, Chapman *et al.* teach one partial amino acid sequence of their molecule (Table 4, Chapman *et al.*). Significantly, this fragment starts at a position equivalent to Applicants' amino acid position 58 and extends well beyond the carboxyl terminal end of Applicants' beta secretase sequence. Thus, Applicants' claims cannot possibly encompass this sequence. Chapman *et al.* do not teach any other fragments, nor do they teach any allelic variant or splice variant sequences of their aspartic proetinase-2. Accordingly, this reference cannot stand as a 102 reference.

In view of the foregoing, Applicants respectfully request reconsideration and removal of the rejection under 35 USC, Section 102.

Rejection Under 35 USC, Section 103

Claims 11 and 17-20 have been rejected as allegedly obvious over Chrysler *et al.* According to the Examiner, "Combining the teachings of Chrysler *et al.* with the high level of knowledge existing in the art at the time the invention was made it [sic] have been obvious to one of ordinary skill in the art to make a pharmaceutical composition of the polypeptide of claim 11 and a fusion protein using the IgG constant domain or its fragment. One would have been motivated to do so as Chrysler *et al.* teach that beta secretase is responsible for the pathogenic cleavage of the of the beta-amyloid precursor protein that has been implicated in the causation of Alzheimer's disease." (page 16 of Official Action dated 14 August 2000).

In response, Applicants respectfully submit that Chrysler *et al.* could not have rendered Applicants' claimed invention obvious at the time it was made. As discussed above, Chrysler *et al.* provide no amino acid or DNA sequence for the beta-secretase enzyme that is the subject of Applicants' invention. Without

such a sequence, the skilled artisan could not have prepared the compounds of Applicants' claims 11 and 17-20, as these claims require as a starting point the full or partial sequence of Applicants' SEQ ID NO:4.

For the reasons set forth above, Applicants respectfully request reconsideration and removal of the rejection under 35 USC, Section 103.

Applicants believe that the claims as presented herein are in condition for allowance, and a notice to that effect is solicited.

Please note that all responsibility for prosecution of this patent application and related applications has been transferred to Richard J. Mazza at Amgen. Accordingly, please send all future communications to Mr. Mazza at the address stated below.

The Commissioner is hereby authorized to charge any filing fees which may be required or credit any overpayment to Deposit Account No. 01-0519 in the name of Amgen Inc.

Respectfully submitted,

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